I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450, ON THE DATE INDICATED BELOW.

BY: _____ Date: 7/26/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	Patent Application of Peter James Watts	:	Group Art Unit 1616
Conf. No.:	1775	:	
Appln. No.	09/269,903	:	Examiner: Frank I. Choi
Filed:	May 6, 1999	:	
For:	COLONIC DELIVERY OF WEAK ACID DRUGS	:	Attorney Docket No. 10774-40US (P-0093)

SECOND DECLARATION OF DR. PETER JAMES WATTS UNDER 37 C.F.R. § 1.132

The following is an overview of this Declaration:

- Paragraphs 1 to 8 relate to my background, expertise, and credentials.
- Paragraphs 9 to 11 relate to the field of the invention and the level of skill in the art at the time of the earliest priority date of the application.
- Paragraphs 12 to 16 describe the Invention.
- Paragraphs 17 to 29 discuss the Examiner's rejections and the absence of a need to undertake undue experimentation in the practice of the claimed invention
- Paragraphs 30 to 36 address the Hardy reference, demonstrating that it does not support a finding of unpredictability.

I, Peter James Watts, declare and state as follows:

Relevant Professional Credentials and Expertise

1. I am a co-inventor of the invention described and claimed in the above-identified patent application ("the Patent Application").

2. I am currently Director, Pharmaceutical Development at West Pharmaceutical Services Drug Delivery and Clinical Research Centre, Ltd. ("West"), in Nottingham, United Kingdom

3. I have worked in the Formulation Section at West (or DanBiosyst UK, Ltd., West's predecessor) since 1992.

4. I have earned the following academic credentials:

(a) in 1987, a Bachelor of Science degree in pharmacy with First Class Honors from the University of Aston, Birmingham, United Kingdom, and

(b) in 1992, a Doctor of Philosophy degree in pharmacy from the University of Nottingham, Nottingham, United Kingdom

5. I have been involved in the study of pharmaceutical formulations and related research and development activities at least since 1987, including research carried out at the University of Aston, the University of Nottingham, and West.

6. I am an author of more than thirty peer reviewed, published articles and conference abstracts, all addressing subject matter within the formulation technology area. I have authored a chapter of a book. I am a named inventor of more than ten United States Letters Patent and numerous UK patents and other patents.

7. I am a member of the Royal Pharmaceutical Society of Great Britain, the Controlled Release Society, and the American Association of Pharmaceutical Scientists.

8. Additional information concerning my background and credentials is provided in my *curriculum vitae*, attached hereto at Appendix A.

Field of Technology

9. This invention described and claimed in the patent application relates to the field of pharmaceutical formulations and drug delivery systems.

10. The level of skill in this field is very high. Persons working in this field who would have practiced the invention at the earliest priority date of the Patent Application would likely possess at least an advanced degree (Master's degree or a Doctor of philosophy degree (or its equivalent)) in pharmacy, and/or a medical degree, in addition to relevant scientific and/or clinical training and experience. At minimum, a person working in this field would have taken courses in and studied organic and inorganic chemistry, biochemistry, anatomy, and pharmacology.

11. Persons practicing in the field of pharmaceutical formulations and drug delivery systems are familiar with the range of active agents or drugs that may be included in various formulations and have access to numerous databases, publications and catalogues describing the active agents and drugs, including, for example the Physicians Desk Reference (PDR), the Merck Index; the United States Pharmacopoeia, Martindale, etc.

The Invention

12. The invention described in the Patent Application is a controlled release composition for a drug that possesses at least one free acid group that can be converted into an alkali metal salt.

13. The composition possesses a physical and chemical structure that prevents release of the drug or drugs until the composition reaches a targeted area of the gastrointestinal tract, the terminal ileum or colon.

14. The composition includes at least one pellet. The pellet(s) are made of at least an inner core. The inner core contains a drug. The inner core is coated with a rate controlling membrane.

15. The pellet(s) that contain the coated inner core are either:

(i) coated (individually) with a coating of a polymer that dissolves at a pH of 4.5 or above. The coating is such that the release of the drug is prevented until the composition reaches the terminal ileum or colon following oral administration of the composition; or

(ii) incorporated into a dosage form; the dosage form itself is coated with a coating of a polymer that dissolves at a pH of 4.5 or above for preventing the release of

the drug until the composition reaches the terminal ileum or colon following oral administration of the composition.

16. The drug included in the inner core of the composition is specifically defined as having several distinct characteristics:

(i) it is a drug;

(ii) it has a free acid group (prior to alkali metal salt formation);

(iii) it has a pK_a in a range of 2.0 to 9.0 (prior to alkali metal salt formation);

(iv) it is present in the composition in the form of an alkali metal salt; and

(v) when in the form of an alkali metal salt, the drug has a higher solubility at pH 4.5 to 8.0 than the drug in its free acid form.

The Office Actions

17. I have read the Office Action (dated October 22, 2003; Paper No. 33) and the Advisory Action (dated April 1, 2004) (collectively referred to as "the Office Actions").

18. The Examiner's comments in the Office Actions indicate that he does not believe that the specification enables the claims to their full breadth but rather contends that they are enabled only with respect to the specific drugs listed in the specification, and that a determination of which drugs are included in the claims would require undue experimentation.

19. More precisely, the Examiner contends that it is not within the routine skills of a person in the art the evaluate whether a given compound is a drug that has a free acid group that can be converted to an alkali metal salt and a pK_a of 2.0 to 9.0 and which is present in the claimed composition in the form of an alkali metal salt that itself has a higher solubility over pH 4.5 to 8.0 than the free acid form of the drug over the same pH range. Moreover, the Examiner asserts that, even if a skilled worker could determine which drugs meet the elements of the claim in a routine manner, it would require undue experimentation to determine if the drug was one that is used in the treatment of ulcerative colitis, used in the treatment of Crohn's disease, used in the treatment of irritable bowel syndrome, and/or used in the treatment of inflammatory bowel disease.

20. In this Declaration, I explain that a skilled person in this field would easily and routinely be able to ascertain the drugs used in the claimed invention, and that such

determination would require minimal, if any, experimentation, based upon the disclosures in the specification coupled with the knowledge of the skilled worker in the field.

A Skilled Worker Would Not Need to Engage in Undue Experimentation to Practice the Full Breadth of the Claimed Invention

21. The claims drawn to the inventive composition and method include a "drug." The definition of a drug is well understood in the technology field of pharmaceutical formulations and drug delivery systems, as such term is routinely used throughout the technology field. Indeed, numerous regulatory agencies, textbooks, and treatises directly and indirectly define the term. As would have been understood to a person of skill in the art at the time this invention was made, a drug is a compound that can be used for, *e.g.*, therapeutic and/or diagnostic effects. For example, a drug may be any compound recognized in the Official United States Pharmacopoeia, the official Homoeopathic Pharmacopoeia of the United States, or the official National Formulary, that is intended for diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals, and intended to affect the structure or function of the body of man or of other animals. *See, e.g.*, 21 C.F.R. § 321; Webster's Collegiate Dictionary at page 350.

22. The claims drawn to the inventive compositions and methods include a drug that has a free acid group. It is a matter of rudimentary chemistry to determine whether a drug has a free acid group that permits the drug to be converted to a salt. One can examine the chemical structure of the compound to determine if it has one or more acid groups that are available to be reduced by replacement of a hydrogen of the acid group with a metal or its equivalent. Such low level analysis is well within the purview of a person of skill in the art, who, as discussed previously, has earned graduate degrees in areas that require the study of chemistry to a more advanced level than would be required to carry out this analysis.

23. In addition, there are numerous published sources from which a person of skill in the art would have been able to look up a given compound to determine whether or not it contains a free acid group.

24. The claims drawn to the inventive composition and method include a drug that has a pK_a of 2.0 to 9.0. Determination of pK_a is a simple and routine matter, particularly to a skilled worker in the field. A skilled worker can obtain this value by routine empirical methods such as those described in Physical Pharmacy (A. Martin, J. Swarbrick and A. Cammarata [eds],

Lee & Febiger, Philadelphia, 1983, pages 263-64). yFor example, the pK_a of a compound X can be calculated from the well known equation:

$$pK_a = \log 1/K = \log 10K, \text{ where } K_a = [H^+][A^+]/[HA]$$

The values for H^+ and A^+ can be determined using data obtained by routine titrations.

25. Additionally, pK_a values may be rapidly and economically obtained by sending drug samples to specialist analytical laboratories, such as Sirius Analytical, Forest Row, East Sussex, UK.

26. The claims of the invention recite that the drug is present in the composition in the form of an alkali metal salt. Alkali metals are well known to a person of skill in the art to be those of Group 1A of the Periodic Table of Elements (excluding hydrogen), and including lithium, sodium, potassium, rubidium, cesium, and francium. Thus, a person of skill in the art, in formulating the drug composition of the invention would have been able to determine whether he or she was incorporating a drug in the form of an alkali metal salt.

27. Methods to prepare alkali salts of a drug bearing a free acid group are well known in the art; at least one technique is described in the specification of this Patent Application at page 6, line 9-29.

28. The claims of the invention recite that the alkali metal salt form of the drug has a higher solubility at pH 4.5 to 8.0 than the free acid form of the drug. The solubility comparison can be carried out by a person of skill in the art using routine solubility evaluation protocols. An exemplary solubility protocol is provided, *e.g.,* in Example 2 of the patent application.

29. Thus, a worker of ordinary skill in the art would be have been able to determine whether a specific drug falls within the scope of the claims without undue experimentation.

The Hardy Reference

30. I note in Paper No. 33, the Examiner relies upon the disclosure of Hardy (at page 94) to support his conclusion that the state of the art is "unpredictable." I believe this conclusion to be incorrect and not supported by the disclosure of Hardy. Indeed, for reasons discussed below, the Examiner's position is contradicted by the disclosure of Hardy.

31. I note that the Hardy reference was published in 1989, well before the earliest priority date of the this application. Accordingly, in cannot be said to reflect the "state of the art" at the time thus application was filed (1997 is the earliest priority date).

32. The Examiner has relied on one sentence removed from the context of the 1989 Hardy reference:

> The current, widely accepted compendial test criteria are poorly predictive of release in man, however, and greater thought should be given to the site of drug absorption and the selection of more relevant test media below pH 6.8.

Hardy at 94 (hereinafter "Hardy Text").

33. The Hardy Text is found in the "Conclusion" section of a book chapter entitled "Enteric Coatings and Delayed Time Release," and as such is a summary of some of the topics discussed throughout the entire chapter. The Hardy Text upon which the Examiner relies refers to the section of the chapter entitled "Evaluation *In Vitro*." It is clear from a review of this section that the compendial tests which Hardy characterizes as unreliable are those that use a time test involving disintegration of the test dosage form within one to two hours when the dosage form is placed in a buffer at pH 6.8 or higher (pH 7.5 if the procedure of the of the 1985 United States Pharmacopoeia was followed). Hardy at 87.

34. However, Hardy notes that 1986 United States Pharmacopoeia adopted a more accurate dissolution standard, and the chapter authors advocated that tests using intermediate pHs would provided even more reliable data concerning the behavior of the dosage form *in vivo*.

35. Thus, Hardy on its face does not support the Examiner's conclusion that the state of the art is characterized by unpredictability for (i) Hardy does not reflect the state of the art as of the earliest priority date of the application; (ii) Hardy itself is internally inconsistent with the Examiner's rejection and (iii) Hardy, published in 1989, provides a description of more reliable means of evaluation.

36. Most significant, the inventive compositions' ability to deliver the drug to the terminal ileum or colon was verified using pharmacoscintigraphy, a well known and widely used procedure in which a radiolabeled composition is administered to the test subject and the radioactivity is followed externally by a gamma camera. Blood samples are additionally collected and analyzed for drug content. Analysis of the gamma camera images allows the point of disintegration of the radiolabeled composition to be determined. For example, an intact tablet or capsule will be displayed as a discrete, concentrated source of radiation, which were dispersed into a wider area when the tablet or capsule disintegrates. This is <u>not</u> the test described in Hardy as being unreliable or unpredictable.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that false statements and the like so made are punishable by fine, imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

P. J. Watts

PETER JAMES WATTS

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